

*Opinions, interpretations, conclusions, and recommendations are those of the author and are not necessarily endorsed by the U.S. Army.

Title: *Clostridium difficile* in the Military Population

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Abstract: *Clostridium difficile*, a gram-positive, spore-forming rod bacterium, causes diarrheal morbidity, increases hospitalizations and health care costs. In this 12-year retrospective-cohort, descriptive epidemiological study of DMSS and 5-year retrospective study of HL7, all components of the U.S. active component service member population was studied. 2,953 CDAD incident cases among active component service members were identified. Annual incident rates increased from 3.86 to 24.03 cases per 100,000 person-years. The overall incidence rates were highest among females, the oldest (45+), white, non-Hispanic, and healthcare workers. Rates of CDAD cases increased during the 12-year surveillance period among active component U.S. service members. HL7 data identified 1,505 positive results out of 20,152 tests performed for *Clostridium difficile* between 2010-2014. Certain risk factors may be associated with this increase, such as gender, age, race, and occupation. These findings may warrant further evaluation to define the risk and impact of CDAD on the health of the U.S. active component service member population.

1. Background

Clostridium difficile (*C. difficile*), a gram positive, obligate anaerobic, spore forming rod bacteria, remains one of the major causes of health-care associated diarrhea^{1,2}. From recognition in the 1970's as the cause of pseudomembranous colitis, *C. difficile* impacted the health-care system by extending hospital stays between 3 to 4 days and increasing healthcare costs¹. *C. difficile* proliferates when normal flora of the gastrointestinal tract are suppressed with antibiotics³. Infections range from mild-diarrhea to life-threatening (sometimes fatal) pseudomembranous colitis^{4,5}. The Centers for Disease Control and Prevention even estimate that it is linked to 14,000 deaths annually⁶.

Risk factors for *Clostridium difficile*-associated diarrhea (CDAD) include ages 65 years and older, antibiotic usage and decreased gastric acidity (especially with use of proton pump inhibitors)¹.

Diagnostic criteria include presence of diarrhea (3 or more unformed stools in 24-hours or less) and positive laboratory testing for *C. difficile* (or colonoscopy/histopathology consistent with pseudomembranous colitis)⁷.

Available testing for *C. difficile* includes stool culture, enzyme immunoassay testing for *C. difficile* toxin A and B, and polymerase chain reaction testing⁷. Unformed stool from the patient should be used for testing⁷.

According to the Armed Forces Health Surveillance Center (AFHSC), hospitalizations that included a diagnosis of *C. difficile* have increased nearly 2.5-fold from 2001 to 2010 (1.8 cases to 6.1 cases per 100,000 person-years respectively)⁸. In comparison, rates of other bacterial-caused gastroenteritis during the same time period remained stable⁸. The military may also have of higher risk of CDAD as previous research suggests that patients who travel to foreign nations (such as active component service members) may be more likely to encounter resistant organisms⁹.

Research into the epidemiology of *C. difficile* has been ongoing. A retrospective cohort analysis of all 232 CDAD cases at National Naval Medical Center from 2005 to 2009 (among all components and both ambulatory and hospitalized patients) by Armbruster and Goldkind found an incidence of 2.6-4.3 cases per 1000 hospital admissions and an outpatient incidence of 0.02-0.04 cases per 1000 outpatient visits)¹. Among which the majority were males aged 60 years and older¹. Active component service members represented 20% of the cases¹.

Another retrospective cohort analysis (this one of hospitalized patients at Barnes-Jewish Hospital from January 1, 2003, through December 31, 2003, excluding neonates and hospitalizations <48 hours) by Dubberke and associates compared CDAD diagnosis rates between positive antigen testing and ICD-9 coding². CDAD rates were 16.4 per 1000 hospital admissions by International Classification of Diseases 9th edition (ICD-9) coding and 14.6 per 1000 hospital admissions by toxin assay². They mention that in the absence of toxin assay results, ICD-9 codes can be used to identify and track CDAD rates².

Buchner and Sonnenberg performed a case-control study of the Department of Veterans Affairs' Patient Treatment File (analyzing all inpatients treated at all VA hospitals throughout the United States)⁵. Of the 15,091 cases of CDAD; the majority were white, older and more likely to have multiple co-morbid illnesses⁵. Cases also had longer hospital stays when compared to controls⁵.

To date, there has not been a retrospective cohort descriptive study of CDAD within the active component U.S. Armed Forces (including Coast Guard) utilizing the Defense Medical Surveillance System (DMSS).

This report summarizes counts, rates and trends of incident *Clostridium difficile* medical encounters among active-component U.S. service members over a 12-year surveillance period.

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2. Methods

The surveillance period was January 1, 2003 to December 31, 2014. The surveillance population included all individuals in the active component service of the Army, Navy, Air Force, Marine Corps and Coast Guard. Coast Guard data prior to 2007 was incomplete and thus excluded from the report.

All data used to determine incident CDAD diagnoses were derived from records routinely maintained in the DMSS. These records document both ambulatory encounters and hospitalizations of active component members of the U.S. Armed Forces in fixed military and civilian (if reimbursed through the Military Health System) treatment facilities.

This is a descriptive epidemiological study. Incident diagnosis of CDAD is defined as an ICD-9 code of 008.45 occurring in any diagnostic position during hospitalizations or ambulatory medical encounters. An individual was considered an incident case of CDAD every 60 days (in other words, multiple counts per subject were allowed).

A positive laboratory result was defined as testing positive for *C. difficile* infection with any of the following: Antigen A/B tests, PCR, Culture, and Antibody testing.

3. Results

During the 12-year surveillance period, 2,953 cases of CDAD among the active component service members were identified based on diagnoses recorded in any diagnostic position (Table 1). The overall CDAD rate increased from 3.86 to 24.03 cases per 100,000 person-years (p-yrs) during the study period (Table 1).

Throughout the entire study, the Coast Guard had the highest infection rate (21.04 per 100,000 p-yrs) followed by the Air Force and the Army (Table 1). The rate of CDAD in females was consistently higher compared to men (Table 2). Fluctuation over the 12 year period was noted for CDAD rates by ethnicity, but overall was highest among white non-Hispanics (Figure 3). By age, those 45 years and older had the highest rate of infection when compared to the other age groups (Figure 4).

Active component service members working in healthcare-related occupations had the highest infection rate of infection (Figure 5).

Between 2008 to 2014, there were 53 cases of CDAD were diagnosed in theater (Table 2). Of which 83% occurred in men (Table 7). The majority of the cases (64%) occurred in service members from the Army (Table 7).

Analysis of the hospitalization data revealed that among those hospitalized with a chemistry test (for *Clostridium Difficile*) within 1 week of CDAD diagnosis, acute appendicitis affected the most individuals (307 cases); followed by intestinal infection due to other organisms (277 cases) and ulcerative colitis (273 cases) (Table 6).

When the HL7 data was analyzed, it was found that 20,152 tests for *Clostridium Difficile* were ordered. 1,505 tested positive, 15,617 tested negative (3,030 tests were either cancelled or result could not be determined).

4. Conclusion

This is the first analysis of all components of the active component service members for CDAD over a twelve-year period. Rates of CDAD increased throughout the study period. This appears to be consistent with the civilian population as the literature notes increase in rates of CDAD (estimated at 3-fold incidence increase from the mid 1990's to the mid-2000's)¹.

The increased rate of infections among white non-Hispanic subjects suggests an association between race and infection. This is similar to the Buchner and associates case-control study; which noted an increase in occurrence of *C. difficile* infections among white patients over a 6-year period⁵.

The increased rate of infection among healthcare workers is surprising. One could postulate that workers who are exposed to patients with *C. difficile* infections may be at an increased risk of becoming infected themselves. Perhaps other factors seen in healthcare workers are confounding the results (access to medical providers, age etc.). Although there are no direct studies that addressed occupation and infection, one study by Lanzas and associates found that in order for new colonization of *C. difficile* to be sustained within a hospital, additional persons infected with *C. difficile* are needed¹⁰.

Acute appendicitis ranking first among diagnoses for hospitalized patients receiving *C. difficile* testing surprised the authors. One possible explanation for this finding may be that those admitted with acute appendicitis may be more likely to receive antimicrobial therapy that targets normal enteric flora (allowing *C. difficile* to thrive without competition from other bacteria).

This study had some limitations. Mild or asymptomatic cases of *C. difficile* may have not been tested or diagnosed. Data from the deployed setting may not be complete (lab testing may not have been available in certain combat environments). Some lab results may be incomplete if tests were sent to civilian medical care (which only records the medical encounter but not laboratory testing ordered by civilian medical providers). Also, if an active component service member seeks civilian medical care without notifying healthcare providers from the active component service members than that information may not be recorded within the DMSS. The Coast Guard data may have been skewed by the exclusion of data prior to 2007 (due to incomplete data prior to that point) and artificially increased the rate of infection among them (not to mention they are a smaller service when compared to the others).

Strengths of this study include having access to the DMSS, which allow capture of longitudinal data within the active component service members along with pertinent demographic information. This allowed us to look for potential associations with infections in the active component U.S. Armed Forces.

Additional work and research should be placed in creating a severity measurement tool as there are currently no validated tools to measure severity of infection among patients with CDAD¹. Few surveillance systems exist outside of individual hospitals for tracking CDAD, perhaps expanding those systems nationwide may yield additional data². Further assessing the role of certain variables (age, gender, occupation, and race) may also be useful. Not to mention medications used prior to infection. Enhancing laboratory capabilities closer to combat zones for *C. difficile* infections may also be beneficial both for treatment as well as for future research. Further education of healthcare providers and staff on *C. difficile* impact on medical care and strict adherence to universal precautions against fecal-oral transmitted infections may also be helpful.

As *Clostridium difficile* infection rates continue to increase, we will need to better identify risks factors and potential areas of intervention in order to control it.

References:

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Table 1. Demographic and military characteristics of service members with a medical encounter for C. Diff, active duty, U.S. Armed Services, 2003-2014

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Table 2. C. diff Rates by Gender, U.S. Armed Services, 2003-2014

Sex	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	Overall Rate
Female	4.17	6.51	16.05	21.67	28.95	23.83	26.78	29.19	37.99	42.03	40.19	40.44	26.48
Male	3.81	5.09	10.91	17.89	17.43	16.75	14.21	15.85	19.42	19.66	26.73	21.11	15.74

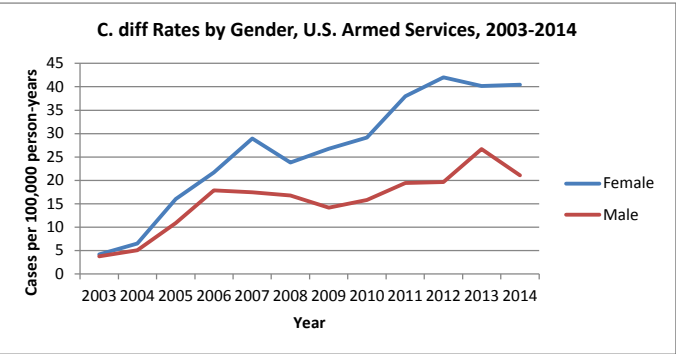


Table 3. C. diff Rates by Ethnicity, U.S. Armed Services, 2003-2014

Ethnicity	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
White, non-hispanic	3.19	4.82	12.37	21.49	20.73	17.77	17.35	20.64	24.73	23.32	30.32	25.32
Black, non-hispanic	3.73	6.94	12.71	16.64	16.25	17.12	15.24	13.86	16.56	19.98	24.68	23.54
Hispanic	4.94	7.61	8.30	11.62	14.20	20.25	12.06	12.45	13.48	24.56	28.79	25.03
Asian/Pacific Is/Other	9.01	1.74	10.45	5.21	19.16	10.45	3.48	8.66	19.07	12.21	22.68	17.37
Unknown	6.54	3.81	7.48	12.08	17.86	19.80	19.07	13.95	27.01	29.65	27.19	16.31

Avg Rate over study period
 18.50368
 15.60461
 15.2755
 11.62436
 16.72841

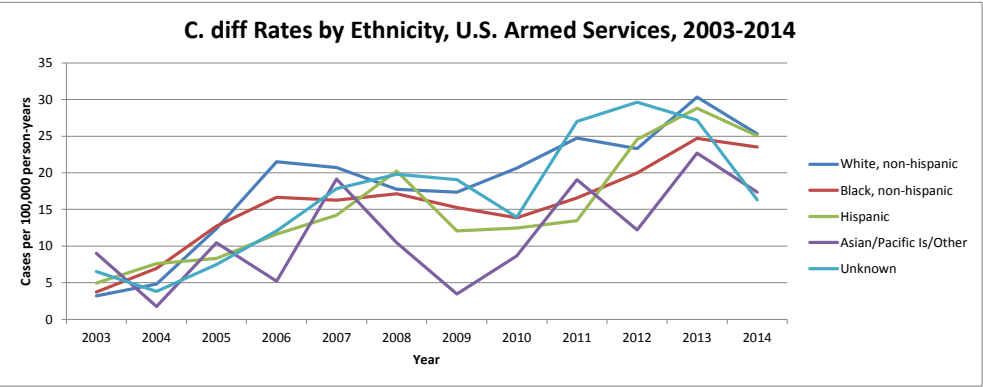


Table 4. C. diff Rates by Age, U.S. Armed Services, 2003-2014

Age	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
17-20	2.26	5.19	9.90	16.59	15.30	17.73	12.31	13.71	27.43	16.15	24.10	18.09
21-25	3.01	4.01	10.54	17.52	13.05	15.26	12.90	16.19	16.13	23.03	27.39	19.51
26-34	3.54	5.80	10.44	18.26	22.90	17.19	16.00	17.21	22.92	20.67	27.51	23.68
35-44	6.47	6.60	13.25	18.91	26.82	22.56	22.11	19.45	26.39	25.07	31.12	30.59
45+	6.44	6.24	31.04	33.02	12.46	20.28	24.77	40.39	29.53	53.80	51.90	50.70

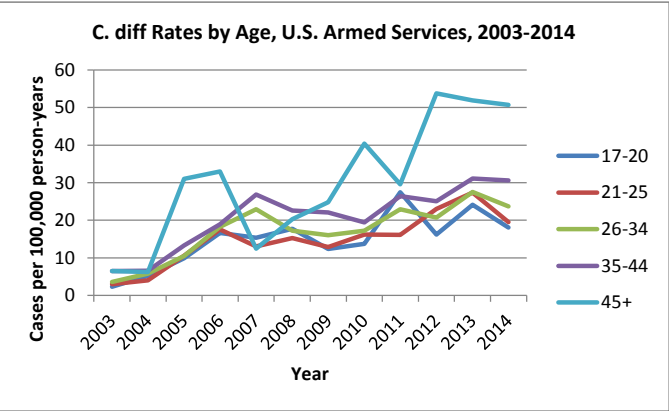


Table 5. C. diff Rates by Occupation, U.S. Armed Services, 2003-2014

Occupatio	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Infantry/Ar tillery/Com bat Engineer	4.30	6.04	4.79	18.46	15.92	18.26	13.56	18.07	20.45	23.24	27.78	14.16
Armor/Mot or Transport	3.30	4.83	18.19	13.55	10.07	16.44	20.76	19.46	27.06	25.54	27.78	20.77
Pilot/Aircr ew	0.00	0.00	12.50	13.04	17.50	12.01	19.57	13.41	26.57	15.05	13.34	11.64
Repair/En gineer	2.91	4.96	9.98	16.16	19.45	15.76	14.62	15.23	20.02	19.10	25.93	17.68
Communic ation/Intelli gence	5.10	4.81	12.35	18.60	21.33	17.41	17.32	18.39	20.25	22.25	30.73	32.05
Healthcar e	6.80	7.59	20.55	31.04	22.55	27.83	25.76	25.67	25.02	36.83	45.54	44.19
Other	3.29	6.20	12.30	18.48	18.81	17.89	12.54	17.64	25.37	23.93	26.88	25.33

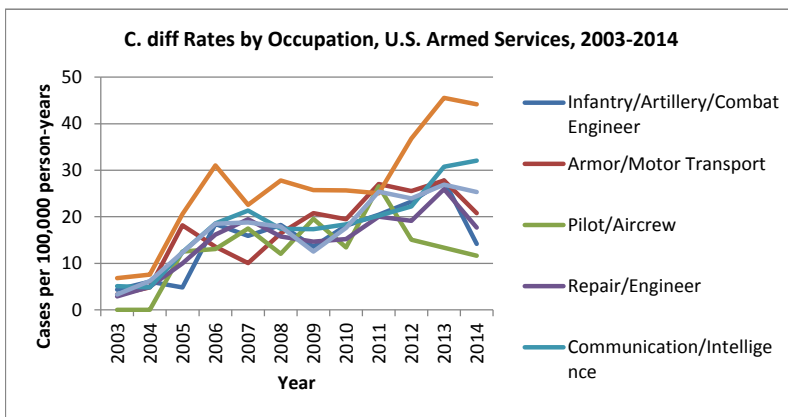


Table 6. Top 10 Hospitalizations among individuals with a chemistry test completed +/- 1 week of C diff diagnosis, all Components, U.S. Armed Services, 2003-2012

Rank	Description	Medical Encounters	Individuals Affected	Bed Days	3 digit dx1
1	ACUTE APPENDICITIS	311	307	1403.00	540
2	INTESTINAL INFECTIONS DUE TO OTHER ORGANISMS	287	277	1104.00	008
3	ULCERATIVE ENTEROCOLITIS	358	273	2240.00	556
4	OTHER AND UNSPECIFIED NONINFECTIOUS GASTROENTERITIS AND COLITIS	273	268	1001.00	558
5	PNEUMONIA ORGANISM UNSPECIFIED	203	194	926.00	486
6	TRAUMA TO PERINEUM AND VULVA DURING DELIVERY	173	173	629.00	664
7	REGIONAL ENTERITIS	170	146	1036.00	555
8	OTHER COMPLICATIONS OF PROCEDURES NOT ELSEWHERE CLASSIFIED	160	146	1158.00	998
9	OTHER CELLULITIS AND ABSCESS	150	144	769.00	682
10	OTHER SYMPTOMS INVOLVING ABDOMEN AND PELVIS	138	136	819.00	789

**3 digit code of primary diagnosis (dx1) only
top 10 by individuals affected**

Table 7. Demographic and military characteristics of service members with a medical encounter for C. Diff in theatre, all components, U.S. Armed Services, 2008-2014

	2008		2009		2010		2011		2012		2013		2014	
	Cases	% Overall	Cases	% Overall	Cases	% Overall	Cases	% Overall	Cases	% Overall	Cases	% Overall	Cases	% Overall
Total	9		7		11		9		7		6		4	
Service														
Army	6	66.67	5	71.43	8	72.73	5	55.56	5	71.43	3	50.00	2	50.00
Navy	1	11.11	0	0.00	0	0.00	1	11.11	0	0.00	1	16.67	2	50.00
Air Force	0	0.00	2	28.57	2	18.18	3	33.33	2	28.57	2	33.33	0	0.00
Marine Corps	2	22.22	0	0.00	1	9.09	0	0.00	0	0.00	0	0.00	0	0.00
Component														
Active	3	33.33	6	85.71	7	63.64	6	66.67	6	85.71	5	83.33	4	100.00
Reserve	3	33.33	0	0.00	0	0.00	2	22.22	1	14.29	1	16.67	0	0.00
Guard	3	33.33	1	14.29	4	36.36	1	11.11	0	0.00	0	0.00	0	0.00
Sex														
Female	1	11.11	1	14.29	3	27.27	2	22.22	1	14.29	1	16.67	0	0.00
Male	8	88.89	6	85.71	8	72.73	7	77.78	6	85.71	5	83.33	4	100.00
Race/ethnicity														
White, non-Hispanic	6	66.67	4	57.14	9	81.82	7	77.78	6	85.71	4	66.67	1	25.00
Black, non-Hispanic	0	0.00	2	28.57	2	18.18	2	22.22	1	14.29	0	0.00	0	0.00
Hispanic	1	11.11	1	14.29	0	0.00	0	0.00	0	0.00	1	16.67	2	50.00
Other	2	22.22	0	0.00	0	0.00	0	0.00	0	0.00	1	16.67	1	25.00
Rank														
E1-E5	7	77.78	4	57.14	5	45.45	5	55.56	4	57.14	5	83.33	2	50.00
E6-E9	0	0.00	3	42.86	4	36.36	4	44.44	1	14.29	1	16.67	2	50.00
O1-O3 & W1-W3	1	11.11	0	0.00	2	18.18	0	0.00	0	0.00	0	0.00	0	0.00
O4-O10 & W4-W5	1	11.11	0	0.00	0	0.00	0	0.00	2	28.57	0	0.00	0	0.00
Age														
<21	0	0.00	0	0.00	1	9.09	1	11.11	0	0.00	0	0.00	0	0.00
21-25	2	22.22	1	14.29	2	18.18	3	33.33	2	28.57	2	33.33	0	0.00
26-34	3	33.33	4	57.14	6	54.55	2	22.22	1	14.29	3	50.00	3	75.00
35-44	4	44.44	2	28.57	2	18.18	2	22.22	1	14.29	1	16.67	0	0.00
45+	0	0.00	0	0.00	0	0.00	1	11.11	3	42.86	0	0.00	1	25.00
Occupation														
Infantry/artillery/combateng	2	22.22	0	0.00	2	18.18	2	22.22	0	0.00	0	0.00	1	25.00
Armor/motortransport	0	0.00	1	14.29	2	18.18	1	11.11	1	14.29	0	0.00	0	0.00
Repair/eng	1	11.11	0	0.00	2	18.18	1	11.11	4	57.14	3	50.00	3	75.00
Comm/intel	2	22.22	6	85.71	4	36.36	4	44.44	0	0.00	1	16.67	0	0.00
Healthcare	1	11.11	0	0.00	0	0.00	1	11.11	0	0.00	1	16.67	0	0.00
Other	3	33.33	0	0.00	1	9.09	0	0.00	2	28.57	1	16.67	0	0.00
Length of Deployment														
<183	1	11.11	1	14.29	4	36.36	3	33.33	0	0.00	1	16.67	0	0.00
183-365	5	55.56	4	57.14	7	63.64	6	66.67	5	71.43	4	66.67	2	50.00
366-547	1	11.11	1	14.29	0	0.00	0	0.00	0	0.00	0	0.00	1	25.00
548+	1	11.11	0	0.00	0	0.00	0	0.00	1	14.29	0	0.00	0	0.00
none found	1	11.11	1	14.29	0	0.00	0	0.00	1	14.29	1	16.67	1	25.00
Operation														
OEF	0	0.00	0	0.00	3	27.27	2	22.22	4	57.14	4	66.67	2	50.00
OIF	8	88.89	6	85.71	8	72.73	3	33.33	0	0.00	0	0.00	1	25.00
OND	0	0.00	0	0.00	0	0.00	4	44.44	2	28.57	1	16.67	0	0.00
none found	1	11.11	1	14.29	0	0.00	0	0.00	1	14.29	1	16.67	1	25.00

**ALL components TMDS only with 60 day incidence rule
closest deploy record used**

Cdiff Frequency by Sex	2008	2009	2010	2011	2012	2013	2014	Total	Total %
Female	1	1	3	2	1	1	0	9	17%
Male	8	6	8	7	6	5	4	44	83%

Cdiff Frequency by Military Br	2008	2009	2010	2011	2012	2013	2014	Total	Total %
Army	6	5	8	5	5	3	2	34	64%
Navy	1	0	0	1	0	1	2	5	9%
Air Force	0	2	2	3	2	2	0	11	21%
Marine Corps	2	0	1	0	0	0	0	3	6%

Table 8. Results of HL7 Tests for *Clostridium Difficile* .

Test results positive for cdiff	1505
Test results negative for cdiff	15617
Test results unknown for cdiff	3030
Total tests	20152

